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(54) Title: PHARMACEUTICAL FORMULATION OF A BETA-LACTAM ANTIBIOTIC AND CLAVULANIC ACID OR A WATER-SOLUBLE SALT THEREOF

(57) Abstract

A pharmaceutical formulation comprising one or more β-lactam antibiotics, clavulanic acid or a water-soluble salt thereof, a pharmaceutically acceptable dicarboxylic acid, and a salt of the dicarboxylic acid in which both acidic hydrogen atoms are replaced by a cation.

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PHARMACEUTICAL FORMULATION OF A BETA-LACTAM ANTIBIOTIC AND CLAVULANIC ACID OR A WATER SOLUABLE SALT THEREOF

This invention relates to pharmaceutical formulations, in particular to formulations containing β-lactam antibiotics and the β-lactamase inhibitor clavulanic acid or derivatives thereof, especially aqueous suspension formulations.

Pharmaceutical formulations containing a β-lactam antibiotic and clavulanic acid or derivatives such as its salts are known. Clavulanic acid in aqueous suspension or solution is known to suffer to some extent from instability, and one significant determinant of stability is the pH of the aqueous medium of the suspension or solution, pH 5.8 - 6.2 being known to be the optimum.

At present the pH of pharmaceutical formulations containing clavulanic acid in suspension or solution is modified by including succinic acid in the formulation. Attempts have been made to further control the pH by the use of buffer salts, but it is found that many commonly used pharmaceutically acceptable buffer salts such as phosphate, citrate, carbonate etc have a catalytic effect deleterious to the stability of the clavulanic acid, and moreover the increased ionic strength of the suspension is also believed to be deleterious to clavulanic acid stability.

This invention provides novel improved pharmaceutical formulations containing clavulanic acid or derivatives thereof in which these problems have to some extent been alleviated, and further unexpected advantages have been achieved.

Accordingly the invention provides a pharmaceutical formulation comprising;

one or more β-lactam antibiotics;

clavulanic acid or a water-soluble salt thereof;

a pharmaceutically acceptable dicarboxylic acid, and;

a salt of the dicarboxylic acid in which both acidic hydrogen atoms are

replaced by a cation.

The formulation may be an aqueous suspension or solution formulation, eg for oral administration or may alternatively be a dry powder, granular or tablet formulation provided primarily for reconstitution into an aqueous suspension or solution formulation.

The one or more β-lactam antibiotics may be penicillins or cephalosporins, especially amoxycillin and ampicillin, preferably amoxycillin in the form of its trihydrate. The clavulanic acid is preferably in the form of one of its salts with a pharmaceutically acceptable cation, especially potassium clavulanate.

Typically the weight ratio of antibiotic: clavulanic acid or clavulanate anion equivalent is in the range 12 : 1 to 1 : 1, suitably 8 : 1 to 1.5 : 1. In an aqueous suspension or solution formulation the concentration of antibiotic and clavulanic acid or clavulanate equivalent will vary depending upon the size of the unit dose in which it is intended to be administered. Typically formulations for oral administration are administered in unit doses of around 5ml spoonfuls or as paediatric drops for small children. Typically the total combined concentration of antibiotic and clavulanic acid or equivalent in such suspensions or solutions may be in the range 25 - 250 mg/ml, for example 30-125 mg/ml. When the formulation is in the form of dry powder, granules or tablets for reconstitution the quantity of antibiotic and clavulanic acid or equivalent may be derived accordingly.

Typical pharmaceutically acceptable dicarboxylic acids are those having a general formula $HOOC.(CH_2)_nCOOH$ wherein n is 1-6 and in which two adjacent (CH_2) groups may be replaced by CH=CH, for example succinic acid, malonic acid, maleic acid and fumaric acid. Of these succinic acid is preferred.

The dicarboxylic acid salt, eg. a succinic acid salt may be of a divalent cation such as calcium or other pharmaceutically acceptable cation, eg of a Group II metal, in which case a single such cation may replace both of the acidic hydrogen atoms. Alternatively each acidic hydrogen atom may be replaced by a monovalent cation such as sodium, potassium or other

pharmaceutically acceptable monovalent cation. Disodium succinate is preferred on account of its low cost, used in combination with succinic acid.

Typically the weight ratio of succinic acid : disodium succinate may be in the range 1 : 50 to 1 : 0.05 representing a molar ratio of succinic acid : succinic acid salt in the range 1 : 33 to 3 : 1. Suitable weight ratios of succinic acid : disodium succinate are around 1 : 30 to 1 : 15, for example 1 : 19 ± 1. Typical weight ranges for other salts may be calculated from these ranges on the basis of the corresponding weight of succinate anion. Typically in an aqueous suspension or solution formulation the total molarity of succinic acid and succinate salt may be in the range 0.001M to 0.01M, suitably 0.001M to 0.0052 M, for example 0.005 ± 0.0001 M. When the formulation is in the form of dry powder, granules or tablets for reconstitution the quantity of succinic acid and succinate salt may be derived accordingly.

The formulation may also optionally contain excipients which may be essentially conventional in the art. For example aqueous suspension or solution formulations may typically contain suspending agents such as Xantham gum, for example 0.25-5 mg/ml, suitably 0.5 - 2.5 mg/ml, thickening agents such as cellulose derivatives, for example 1 - 100 mg/ml if present, sweeteners such as aspartame or equivalent sugars, eg 0.5-5 mg/ml, and flavouring agents such as fruit flavourings and syrup flavourings, eg 10-20 mg/ml etc. Silicas such as "Aerosil" may be present as thickening agents and/or as a powder flow aid, and other silicas such as "Syloid" may be present as an internal dessicant and bulking agent. Typically silicas may be present at eg 1-100 mg/ml. Dry powder, granule or tablet formulations for reconstitution may contain corresponding weights of these and/or other conventional excipients.

Aqueous suspension and solution formulations of this invention may be provided in entirely conventional bottles etc, and dry powder or granule formulations for reconstitution may be provided in conventional jars, sachets etc which are advisedly airtight.

The formulations of the invention appear to offer a number of advantages over known formulations which contain a β-lactam antibiotic in

combination with clavulanic acid or clavulanate equivalent. These include improvement of stability in solution for example by 2-4% of the initial concentration on storage for 7 days at 5°C. The stability in solution is more robust in terms of pH differences in the water used to make up the suspension or solution and the quality of raw materials such as amoxycillin trihydrate. The presence of succinate ion appears to inhibit the colour change from white to pale cream that sometimes follows reconstitution, and there appears to be some enhancement of the flavour of reconstituted suspensions and solutions.

The invention also provides a process for the preparation of such a pharmaceutical formulation, comprising admixing the β-lactam antibiotic, the clavulanic acid or salt thereof, the dicarboxylic acid and the salt thereof, and optionally any excipients, and optionally making the product up with water or an aqueous medium to form a suspension or solution formulation.

The invention also provides a process for the use of a pharmaceutical formulation as described above in the manufacture of a medicament for the treatment of bacterial infections.

The invention also provides a pharmaceutical formulation as described above for use in the treatment of bacterial infections.

The invention also provides a method of treatment of bacterial infections in humans or animals which comprises the administration of a therapeutically effective amount of a pharmaceutical formulation as described above.

The invention will now be described by way of example only. In these examples the abbreviation (fa) as used in connection with amoxycillin trihydrate and potassium clavulanate indicates that the weight is expressed as the equivalent of free acid, ie respectively amoxycillin and clavulanic acid.

Example 1

Amoxycillin/Clavulanate Suspension

Ingredient	mg per 100ml
Amoxycillin trihydrate	2500.0 (fa)
Potassium clavulanate	656.25 (fa)
Xanthan gam (Keltrol T)	250.0
Aspartame	250.0
Colloidal silica (Aerosil 200)	500.0
Silicon dioxide (Syloid ALI)	2500.0
Methocel E5	3000.0
Succinic acid	2.95
Disodium succinate	76.97
Raspberry dry flavour (Naarden)	450.0
Orange dry flavour (P.F.W.)	300.0
Orange dry flavour (Dragoco)	225.0
Golden syrup flavour (Fermenich)	475.0

A unit dose of 5ml of this suspension contains 156 mg of amoxycillin/clavulanic acid combination.

Example 2

Amoxycillin/Clavulanate Suspension (Paediatric Drops)

Ingredient	mg per 30 ml
Amoxycillin trihydrate	3000.0 (fa)
Potassium clavulanate	393.75 (fa)
Xanthan gam (Keltrol T)	50.0
Aspartame	75.0
Colloidal silica (Aerosil 200)	75.0
Silicon dioxide (Syloid ALI)	750.0
Succinic acid	1.0
Disodium succinate (Anhydrous)	23.1
Raspberry dry flavour (Naarden)	135.0
Orange dry flavour (P.F.W.)	90.0
Orange dry flavour (Dragoco)	67.5
Golden syrup Dry flavour (Fermenich)	143.0

This suspension contains 112.5 mg per ml of amoxycillin/ clavulanic acid combination.

Exampl 3

Amoxycillin/Clavulanate Suspension

Ingredient	mg per 100 ml
Amoxycillin trihydrate	5000.0 (fa)
Potassium clavulanate	1312.5 (fa)
Xanthan gam (Keltrol T)	250.0
Aspartame	250.0
Colloidal silica (Aerosil 200)	500.0
Silicon dioxide (Syloid ALI)	2500.0
Methocel E5	3000.0
Succinic acid	2.95
Disodium succinate	76.97
Raspberry dry flavour (Naarden)	450.0
Orange dry flavour (P.F.W.)	300.0
Orange dry flavour (Dragoco)	225.0
Golden syrup flavour (Fermenich)	475.0

A unit dose of 5 ml of this suspension contains 312 mg of amoxycillin/clavulanic acid combination.

The above three suspensions were made up in an entirely conventional manner by adding the ingredients to cold water and stirring. Shaking of the reconstituted suspension immediately prior to administration was found to be desirable to ensure resuspension.

Example 4

Amoxycillin/Clavulanate Suspension

Ingredient	mg per 100ml
Amoxycillin trihydrate	2500.0 (fa)
Potassium clavulanate	1312.5 (fa)
Xanthan gam (Keltrol T)	250.0
Aspartame	250.0
Colloidal silica (Aerosil 200)	500.0
Silicon dioxide (Syloid ALI)	2500.0
Methocel E5	3000.0
Succinic acid	2.95
Disodium succinate	76.97
Raspberry dry flavour (Naarden)	450.0
Orange dry flavour (P.F.W.)	300.0
Orange dry flavour (Dragoco)	225.0
Golden syrup flavour (Fermenich)	475.0

A unit dose of 5ml of this suspension contains 187 mg of amoxycillin/clavulanic acid combination.

Claims

1. A pharmaceutical formulation comprising;
one or more β-lactam antibiotics;
clavulanic acid or a water-soluble salt thereof;
a pharmaceutically acceptable dicarboxylic acid, and;
a salt of the dicarboxylic acid in which both acidic hydrogen atoms are replaced by a cation.

2. A pharmaceutical formulation according to claim 1 wherein the β-lactam antibiotic is amoxycillin or ampicillin.

3. A pharmaceutical formulation according to claim 1 or 2 wherein the clavulanic acid is in the form of potassium clavulanate.

4. A pharmaceutical formulation according to any one of the preceding claims wherein the ratio of antibiotic : clavulanic acid is in the range 12 : 1 to 1 : 1.

5. A pharmaceutical formulation according to any one of the preceding claims wherein the dicarboxylic acid has a general formula $HOOC.(CH_2)_n.COOH$ wherein n is 1-6 and in which two adjacent (CH_2) groups may be replaced by CH = CH.

6. A pharmaceutical formulation according to claim 5 wherein the dicarboxylic acid is selected from succinic acid, maleic acid, malonic acid and fumaric acid.

7. A pharmaceutical formulation according to any one of the preceding claims wherein the dicarboxylic acid salt is of a divalent cation which replaces both acidic hydrogen atoms.

8. A pharmaceutical formulation according to any one of claims 1-6 in which in the salt of the dicarboxylic acid each acidic hydrogen atom is replaced by a single monovalent cation.

9. A pharmaceutical formulation according to claim 8 wherein the salt of the dicarboxylic acid is disodium succinate.

10. A pharmaceutical formulation according to claim 9 wherein the molar ratio succinic acid : disodium succinate is in the range 1 : 33 to 3 : 1.

11. A pharmaceutical formulation according to claim 9 or 10 being an aqueous solution or suspension and having a total molarity of succinic acid and succinate salt in the range 0.001M to 0.01M.

12. A pharmaceutical formulation according to any one of the preceding claims substantially as hereinbefore described with reference to examples 1 to 4.

13. A process for the preparation of a pharmaceutical formulation as claimed in any one of claims 1 to 12, comprising admixing the β-lactam antibiotic, the clavulanic acid or salt thereof, the dicarboxylic acid and the salt thereof, and optionally any excipients, and optionally making the product up with water or an aqueous medium to form a suspension or solution formulation.

14. A process for the use of a pharmaceutical formulation as claimed in any one of claims 1 to 12 in the manufacture of a medicament for the treatment of bacterial infections.

15. A pharmaceutical formulation as claimed in any one of claims 1 to 12 for use in the treatment of bacterial infections.

16. A method of treatment of bacterial infections in humans or animals which comprises the administration of a therapeutically effective amount of a pharmaceutical formulation as claimed in any one of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

PCT/GB 92/01207

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/43; A61K47/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A,P	WO,A,9 115 197 (BEECHAM GROUPE PLC) 17 October 1991 see claims 1,2,11	1-16
A	EP,A,0 080 862 (BEECHAM GROUP PLC) 8 June 1983 see page 2; example 1	1-16

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 OCTOBER 1992	20. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT FFICE	DEGUELDRE A. J. J.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201207 SA 61585

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/10/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9115197	17-10-91	AU-A- 7558691	30-10-91
EP-A-0080862	08-06-83	AU-A- 9103782	09-06-83
		JP-C- 1580055	13-09-90
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